UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/673,302	LAW ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-68 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-68 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 23 March 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 1-68 are pending and being examined on the merits.

Priority

It is noted that this application appears to claim subject matter disclosed in prior copending applications, Application No. PCT/US99/08285, filed 04/15/1999, and Application No. 60/115,516, filed on 04/15/1998. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-24 are rejected under 35 U.S.C. 101 because the claims read on non-human mammals comprising naturally occurring mutations of the GP IIIa gene, where one of the cytoplasmic tyrosine residues encoded by the gene has been replaced with a non-tyrosine residue.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification teaches a mutant murine GP IIIa gene where at least one of the two cytoplasmic tyrosine residues (747 and 759) has been replaced with a phenylalanine residue, and mice comprising the mutant GP IIIa gene, however, the specification fails to describe any other species within the genus of mutant GP IIIa genes from any species, where at least one of the two cytoplasmic tyrosine residues encoded by the gene has been replaced with any other non-tyrosine residue, encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective**

filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of any mutant GP IIIa gene where at least one of the two cytoplasmic tyrosine residues encoded by the gene has been replaced with any non-tyrosine residue lacks a written description. The specification fails to describe what mutant GP IIIa genes fall into this genus when constructed and used as claimed. The skilled artisan cannot envision all such mutant GP IIIa genes, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the described mutant murine GP IIIa gene where at least one of the two cytoplasmic tyrosine residues (747 and 759) has been replaced with a phenylalanine residue, meet the written description provision of 35 U.S.C. § 112.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a non-human mammal and methods of making a non-human mammal expressing a transgene stably introduced into its DNA, wherein the transgene comprises DNA encoding mutant GP IIIa where at least one of the two cytoplasmic tyrosine residues has been replaced with a non-tyrosine residue and methods of using the same.

The specification teaches the production and use of a transgenic mammal in which the endogenous GP IIIa gene (also known as β3) has been replaced in whole or in part with a mutant GP IIIa gene, where one or both of the two phosphorylatable cytoplasmic tyrosine residues have been replaced with non-tyrosine residues (see p 1, lines 11-17). The specification specifically teaches that the murine GP IIIa gene was isolated and the two tyrosine residues 747 and 759 were mutated to phenylalanine

using standard site-directed mutagenesis (see examples 1-2). The specification teaches that the mutated GP IIIa DNA was then subcloned into a targeting vector containing a neomycin resistant cassette, and the neo^r DNA was flanked by FRT recognition sequences (see example 3). The targeting construct was then transfected into murine ES cells and positive clones were identified (see example 4). The ES cells that contained the mutant GP IIIa DNA were then injected into blastocytes and implanted into pseudo-pregnant foster mothers. The male chimeric mice were identified and mated with wild-type females. The heterozygote offspring were then further mated to produce homozygote animals. The specification teaches that the resulting mice are viable and express GP IIB-IIIa on their platelets at similar levels to that seen in normal animals expressing non-mutant GP IIIa (see p. 22, lines 8-12).

However, the specification fails to provide an enabling disclosure for the preparation of the exemplified transgenic mice exhibiting an appropriate phenotype. Because the specification discloses no phenotype for the exemplified mice, undue experimentation would have been required for one of skill in the art to make and/or use the claimed invention. To this end, the specification does not provide guidance for any particular phenotype for the described mice, other than the anticipated expression of the transgene.

Note that the mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well developed for a number of species, and in particular, the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well

established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends upon the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessary achieve the same result in a rat. This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, birds, cows, fish, pigs, etc., which can affect the phenotype in an unpredictable manner. With the limited working examples, the existence of any phenotypic alteration resulting from the introduction of a mutant GP IIIa construct in any species of animal, other than the mouse, is highly unpredictable.

The state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic

animals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph): *e.g.*, specific promoters, presence or absence of introns, *etc.* As such guidance is lacking in the instant specification, it fails to feature any correlation between the expression of any mutant GP IIIa gene, other than the exemplified mutant gene, in any host animal, other than the exemplified mouse, and, thus, a specific resulting disease phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice

exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of any other non-human mammal comprising a mutant GP IIIa gene, where one of the two cytoplasmic tyrosine residues has been replaced by a non-tyrosine residue, it would have required undue experimentation to predict the results achieved in any one host animal comprising and

expressing such a transgene, the levels of the transgene product, the consequences of that production, and therefore, the resulting phenotype.

The specification fails to provide an enabling disclosure for the preparation of any transgenic animals harboring any mutant GPIIIa gene, because the guidance offered in the specification is not sufficient to teach one skilled in the art as to how to prepare the claimed transgenic animals exhibiting an appropriate phenotype. Since homologous recombination is required for the gene targeting methods, such as those employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out this method. The state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, *Summary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

> "The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of <u>any</u> species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal.

In addition, prior to the time of filing, Mullins *et al.* (**Journal of Clinical Investigation**, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only **mouse ES cells** were available for use for production of transgenic mice.

The specification discloses no phenotype for the claimed transgenic animals, other than the anticipated expression of the transgene. There is no demonstration that the claimed animals would in fact exhibit a phenotype useful for the claimed methods of use of the transgenic animals. Without knowing the phenotype of the transgenic mouse, sheep, goat, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow or guinea pig, one of skill in the art would not know how to use the animal.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of any species of transgenic mammal in methods of comparing platelet function and methods of screening, but the specification does not enable this use. In the absence of disclosure of a transgenic animal exhibiting the appropriate phenotype, undue experimentation would have been required to make

and/or use the claimed transgenic non-human mammals and methods of using the same.

Accordingly, in view of the quantity of experimentation necessary for the production and methods of use of any non-human mammal and methods of making a non-human mammal expressing a transgene stably introduced into its DNA, wherein the transgene comprises DNA encoding a mutant GP IIIa where at least one of the two cytoplasmic tyrosine residues has been replaced with a non-tyrosine residue, the unpredictable and undeveloped state of the transgenic and ES art, and particularly with respect to the unpredictable nature of the phenotypic effect, it would have required undue experimentation for one skilled in the art to make and/or use the claimed transgenic non-human mammals and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written, is vague and confusing. The claim recites the term, "the gen" in line 2 of the claim. It is unclear if "the gene" refers to a mutant gene or wildtype gene Correction/clarification is requested. Claims 2-12 depend on claim 1.

Claim 13, as written, is vague and confusing. The claim recites the term "DNA". It is noted that DNA can refer to either genomic and mitochondrial DNA. It is suggested

that the claim be rewritten to state, "a transgene stably introduced into its genome ..." Claims 14-24 depend on claim 13.

Claim 25, as written, is vague and confusing. The claim recites the term "regenerating" in part (b) of the claim. It is unclear how a transformed non-human mammal can be regenerated if it has not yet been generated. It is suggested that the claim be rewritten to state, "generating a transformed ..." Claims 26-36 depend on claim 25.

Claim 37, as written, is vague and confusing. The claim recites the term "regenerating" in part (e) of the claim. It is unclear how a transformed non-human mammal can be regenerated if it has not yet been generated. It is suggested that the claim be rewritten to state, "generating a transformed non-human mammal from the blastocysts of step d), wherein the transformed non-human mammal is chimeric for the mutan GP IIIa gene." Claims 38-50 depend on claim 37.

Claims 27, 32, 39, 44, 53 and 58 recite the limitation "the cytoplasmic tyrosine residues" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 30, 42, and 56 recite the limitation "cytoplasmic tyrosine residues" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim. Claims 31-34 depend on claim 30.

Claim 51 is drawn to methods, but no clear and defined steps are recited in the independent claims. Phrases such as "comparing a characteristic mediated by platelet function" are vague and do not set forth a defined method. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active

fashion. See Ex Parte Erlich, 3 USPQ2d. p. 1011 (Bd. Pat. App. Int. 1986). Claims 52-66 depend on claim 51.

Claim 61 recites the limitation "the bleeding time" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claims 61-65 recite the limitation "the two mammal types" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 62 recites the limitation "the thrombotic responses" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 67 recites the limitation "the mammal" in part (a) of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 68 depends on claim 67.

Claim 67 recites the limitation "said administration" in part (b) of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 68 depends on claim 67.

Claim 67 recites the limitation "the administration" in part (c) of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 68 depends on claim 67.

Claim 68 recites the limitation "the mammal" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

TNT

Thaian N. Ton
Patent Examiner
Group 1632